MONITORING OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN TYPE 2 DIABETES MELLITUS PATIENTS MAY REDUCE THE MORTALITY

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INTRODUCTION

C-reactive protein is an acute phase protein present in the blood of acutely ill patients. It consists of five identical nonglycosylated polypeptide subunits non-covalently bound to form a disk shaped cyclic polymer with a molecular weight of about 115 KDa.¹ This alpha globulin is synthesized in the liver under the control of interleukin-6. Formation of fatty streak on endothelial cells on any grade of infection cause recruitment of leucocytes triggered by inflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha. The primary pro-inflammatory cytokines such as CD-40 influence the expression of messenger cytokines such as interleukin-6, which travel from local sites of inflammation to the liver where a change in the programme of protein synthesis of the acute phase response occurs.²,³

This acute phase protein binds with the cell wall C-polysaccharide of Streptococcus Pneumoniae and agglutinate the organism and so named as C-Reactive Protein (CRP). CRP acts as nonspecific host defense, especially against infection and inflammation.¹ Elevated value of CRP is found in wide range of acute or chronic illness like gram positive and gram negative infection, trauma, rheumatoid arthritis, tuberculosis etc. In acute stage of infection CRP level increases to peak within 48 hours as much as 1000 folds.² It requires the use of high sensitivity CRP (hsCRP) assay having detection limit less than 0.03 mg/L.⁷

Chronic inflammation is an important factor for the development and progression of atherosclerosis. Different studies have revealed the fact that there is a strong positive association of CRP with the risk of future coronary events like coronary artery disease, peripheral artery disease and cerebrovascular disease.⁴,⁵,⁶ It requires the use of high sensitivity CRP (hsCRP) assay having detection limit less than 0.03 mg/L.⁷

Association of cardiovascular events with type-2 Diabetes Mellitus is an established fact and they have 2-4 fold high risk for CHD. The present study aimed at finding the relation of the hsCRP with the type-2 Diabetes Mellitus in Tripura state. Low grade chronic infection leads to moderate rise in hsCRP levels. Diabetic patients are more susceptible in this regard. Atherogenesis has also got a positive correlation with the chronic infection. Elevated levels of hsCRP predict not only cardiovascular events, but also the onset of type-2 diabetes mellitus, probably because hsCRP levels correlate with several components of metabolic syndrome including those not easily measured in clinical practice such as insulin sensitivity, endothelial dysfunction and hypo fibrinolysis.⁸,⁹,¹⁰

In major studies from the United States and Europe, hsCRP levels predicted subsequent risk better than LDL-cholesterol levels.¹¹,¹² According to Adult Treatment Panel (ATP III), hsCRP levels less than 1, 1 to 3 and greater than 3 mg/L define as low, moderate and high risk groups respectively for future vascular events. Mortality rate increases when hsCRP levels is more than 3 mg/L. Therefore, hsCRP could be a predictor of the risk factor of cardiovascular events.

MATERIALS AND METHODS

CRP has been measured with the detection level of 3mg/L, which is not sensitive enough to detect lower level value for prediction of cardiovascular risk. For this, high sensitive immunoturbidimetric method is used to detect the lower level near to 0.3mg/L. It is based on the light scattering properties of the antigen-antibody complex formed by the covalently coupling latex particles to a specific antibody and useful to detect very low level of CRP.⁸

The present study was conducted with 150 number of Diabetes Mellitus type-2 patients who have been suffering for more than 10 years. All of them are either under oral hypoglycemic drugs or Insulin. Their ages were 45 years and above. Equal number of persons were selected for study as control. Along with hs-CRP, lipid profile and Serum urea, Creatinine values were also estimated and the patients with their normal values were selected for the study.

RESULT

In this study serum of total 150 known type 2 diabetic patients were assayed for hs CRP by immunoturbidometry method after observing all formalities. Equal number of normal
persons were also taken for the estimation of hs-CRP. Estimation of lipid profile, urea and creatinine were done for all the patients and the normal individual. Among them 85(56.67%) patients were male and 65(43.33%) were female. The result has been divided into three groups – one group having hsCRP levels less than 1 mg/L; other group having hsCRP levels between 1.1-3mg/L and the group having hsCRP value 3.1-10 mg/L. In case of male patients, it shows that hsCRP value of 57 (67.06%) patients had less than 1mg/L, 23 patients (27.06) had 1.1-3mg/L and only 5 patients (5.88%) patients had in the range of 3.1-10mg/L. The mean value was 1.25±1.27 and p-value was 0.0037, which is very sensitive.

In case of females 42 (64.62%) patients had <1mg/L, 19 (29.23%) patients had in the range of 1.1-3mg/L and only 4 (6.15%) patients between 3.1-10mg/L. The mean value was 1.29±1.30 and p-value was 0.0074, which was again very sensitive. The hs-CRP value of total 66% of the patients had less than 1mg/L, 28% had 1-3mg/L and only 6% had 3.1-10mg/L with the mean value 1.29 ± 1.30 and p-value 0.0001. It is highly sensitive.

It also shows that hs-CRP does not have any relation with the sex of the patients. So far the age is concern patients of 45-55 years of age group had no cardiac symptoms. All of those patients above 65 years with cardiac involvement were suffering from T2DM for more than 15 years. Total 7.33% of diabetic patients with high hs-CRP value showed cardiac involvement in ECG.

SUMMARY
The hs-CRP level of a person increases in all sorts of acute inflammatory and infectious cases which subsides when the acute phase is over. But persistent moderately higher level of hs CRP is found to be a risk factor for coronary heart disease. The present study in Tripura shows that 7.33% of T2DM. Patients had a marginal higher value of hs-CRP. The higher value is independent of sex, serum lipid profile and renal status, male (p value 0.0037) and female (p value 0.0074). Duration of T2DM and age of the patients had a positive correlation. The patients of 56-65 years of age group had 3.45% of cardiac involvement and the patients of T2DM with more than 15 years duration and above 65 years had higher cardiac involvement (44.44%). These patients are at higher risk than those of normal hs-CRP.

CONCLUSION
From this study in Tripura, it can be concluded that 7.33% of T2DM patients had a marginal higher value of hs-CRP and higher the duration of Diabetic Mellitus with the increased age (more than 65 years), higher is the cardiac involvement (44.44%). There is no relation with the sex, serum lipid profile and renal status of the patients in this regard. Therefore, hs-CRP can be a marker of CAD for the patients of T2DM. If the hs-CRP is evaluated for the patients of in T2DM frequent intervals and those patients with higher hs-CRP can be screened and effective measures are taken, mortality and morbidity due to CAD can be controlled.

REFERENCES

<table>
<thead>
<tr>
<th>Age (In years)</th>
<th>Controls N (%)</th>
<th>Known Diabetics [N=150]</th>
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<tr>
<td></td>
<td>Non-cardiac N (%)</td>
<td>Cardiac N (%)</td>
</tr>
<tr>
<td>45-55</td>
<td>48 (32)</td>
<td>45 (100)</td>
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<tr>
<td>56-65</td>
<td>67 (44.67)</td>
<td>84 (96.55)</td>
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<td>66 and above</td>
<td>35 (23.33)</td>
<td>10 (55.56)</td>
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<td>Total</td>
<td>150 (100)</td>
<td>139 (92.67)</td>
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Table 1: Age distribution of study subjects (diabetic non-cardiac and cardiac patients) and gender matched healthy controls.
<table>
<thead>
<tr>
<th>Gender</th>
<th>Total N (%)</th>
<th>hs-CRP Level - Diabetics [N=150]</th>
<th>hs-CRP [Mean ± SD]</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 1mg/L</td>
<td>1-3 mg/L</td>
<td>3.1-10 mg/L</td>
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<tr>
<td>Male</td>
<td>85 (56.67)</td>
<td>57 (67.06)</td>
<td>23 (27.06)</td>
<td>5 (5.88)</td>
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<tr>
<td>Female</td>
<td>65 (43.33)</td>
<td>42 (64.62)</td>
<td>19 (29.23)</td>
<td>4 (6.15)</td>
</tr>
<tr>
<td>Total</td>
<td>150 (100)</td>
<td>99 (66)</td>
<td>42 (28)</td>
<td>9 (6)</td>
</tr>
</tbody>
</table>

Table 2: Gender distribution and hs-CRP level among study subjects and controls

(Student’s T-test for 2 independent means, one-sided p value, 95% confidence interval)

Fig. 1: Correlation of age (In years) and hs-CRP (In mg/L) among study subjects (R²=0.235) [N=150]